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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	

ART UNIT	PAPER NUMBER
1652	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/518,223	CHENG ET AL.	
	Examiner	Art Unit	
	Iqbal H. Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *24,26-29,32 and 35-37* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *24, 26-29, 32, 35-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 24, 26-29, 32, and 35-37 are currently pending.

This application is a 371 of PCT/GB03/02665.

The preliminary amendment filed on 7/6/2007, amending claims 24, 26-29, 32,canceling claims 25, 30-31, 34 and adding new claims 35-37 is acknowledged. Claims 1-23 were previously cancelled.

Claims 24, 26-29, 32 and 35-37 are under consideration and will be examined herein.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/8/2007 has been entered.

Applicants' arguments filed on July 6, 2007 have been fully considered but are not deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Priority

Acknowledgement is made of applicants claim for foreign priority of application CHINA PCT/CN02/00635 filed on 9/9/2002.

Information Disclosure Statement

The information disclosure statements (IDS) submitted on 3/10/2006 and 7/14/2006 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are considered by the examiner.

Drawings

Drawings submitted on 12/15/2004 are accepted by the Examiner.

Claim Objections

Claim 24 is objected to in the recitation "administering isolated" should be "administering an isolated". Appropriate correction is required.

Claim 24 is objected to in the recitation "wherein said arginase comprising chemical modification" should be "wherein said arginase comprises a chemical modification". Appropriate correction is required.

Claim 24 is objected to in the recitation "half-life for" should be "half-life of". Appropriate correction is required.

Claim 28 is objected to in the recitation "treatment malignancies", which is grammatically incorrect, should be "treating malignancies". Appropriate correction is required.

Claim 29 is objected to in the recitation "of protein" should be "of a protein". Appropriate correction is required.

Claim 32 is objected to in the recitation "comprising isolated" should be "comprises an isolated ---". Appropriate correction is required.

Claim 36 is objected to in the recitation "of protein" should be "of a protein". Appropriate correction is required.

Maintained-Claim Rejections - 35 U.S.C. § 112(2)

Previous rejection of Claims 29 and 36 under 35 U.S.C. 112, second paragraph, in the recitation of "method is performed in absence of protein breakdown inhibitor" is maintained. Applicants argue that said inhibitors indeed mean commercially available drugs capable of decreasing proteolysis. However, claim still recites the phrase whose metes and bounds are not clear. Therefore, the rejection is maintained.

Maintained-Claim Rejections - 35 USC § 112(1)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Previous rejection of Claims 24, 26-29, 32 and 35-37 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in the previous office action. It is maintained for the reasons of record and discussed below.

Claims 24, 26-29, 32 and 35-37 are directed to a method of treatment of human malignancies, comprising administering an isolated and purified recombinant human arginase I to a patient, wherein said arginase comprises any chemical modification resulting in a specific

activity of at least 336 I.U/mg, a purity of >80% and extended half-life of at least 3 days or any composition comprising any modified arginase I or any composition that reduces the physiological arginine level.

Applicants argue that they have amended Claim 24 and 32 to recite a chemically modified, isolated and purified recombinant human arginase I having a specific activity of at least 336 I.U./mg, a purity of 80-100% and an extended half-life of at least 3 days and further argue that the lack of written description rejection must be made with "findings of fact which support the lack of written description conclusion. These findings should A) identify the claim limitation at issue and B) establish a prima facie case by providing reasons why a person skilled in the art at the time the application was filed would not have recognized that the inventor was in possession of the invention as claimed in view of the disclosure of the application as filed". Applicant states: A. The claim limitation is a chemically modified, isolated and purified recombinant human arginase I having a specific activity of at least about 336I.U./mg, an extended half-life of at least 3 days and of 80-100% purity and thus the arginase I in the aforesaid claims does not mean "any modified arginase I". Not all kinds of modification would result in such a high specific activity, purity and extension of halt-life, and those modifications that do not achieve the above-specified claim limitations would not be included into the scope of these claims. B. According to MPEP 2163 I, "an applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations ----". Applicant submits that disclosure of preparation of recombinant human arginase 1 (see Example 1 to 7), pegylation of the arginase I (see Example 8A to 8C), half-life determination of the arginase I (see Examples 9A to 9B), and a method of treatment using the modified arginase I (see Example 11 to 18)

clearly shows possession of the "isolated and purified recombinant human arginase I" modified to have "a specific activity of at least 336 I.U./mg, a purity of 80-100% and an extended half-life of at least 3 days" as claimed. Applicants further argue that one skilled in the art would be able to reproduce the invention by following the aforesaid procedures and the present application has thus fulfilled the requirements of adequate written description requirement (see MPEP 2163 II.3 (a)). Applicant therefore submits that examiner has failed to establish a prime facie case of lack of written description.

Applicant's arguments have been fully considered but are not persuasive to overcome the Written description rejection.

The Examiner acknowledges addition of new limitations such as "isolated and purified", and "chemical modification", however the amendment does not give enough structural description of the chemical modifications in any human arginase I, which would result in the recited characteristics i.e., extended half-life. Proteins can be modified by many different means, which result in very different characteristics. If applicants were to limit the claims to the modification disclosed in the specification then the genus of polypeptides will be adequately described. In addition, claims 28, 29 and 37 are drawn to a pharmaceutical composition comprising any unknown agent that would reduce physiological arginine level to less than 10 uM. However, there is no description of the entire genus of compounds, which would reduce physiological arginine levels less than 10 uM or which ones can be used for treating malignancies as claimed.

As discussed in the written description guidelines, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of

species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. A representative number of species means that the species, which are adequately described are representative of the entire genus. **Thus, when there is substantial variation within the genus, one must describe a sufficient structure and variety of species to reflect the representative structure variation within the genus.** Satisfactory disclosure of a representative structure and number depends on whether one of skill in the art would recognize that the applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus in view of species disclosed. For inventions in an unpredictable art, adequate written description of a genus cannot be achieved by disclosing the structure of small portion of only one species within the genus. The genus of modified human polypeptides having arginase activity is potentially structurally diverse as it broadly encompasses many kinds of chemical modifications and human polypeptides having different structures. Also, the claims encompass a genus of compounds of completely unknown structure that would reduce arginine levels to less than 10 uM for 3 days ~~for using as a composition~~ (claim 28 and 29). As such, the disclosure solely of functional features coupled with minor structural features that may or may not present in all members of the genus is insufficient to be representative of the attributes and features of the entire genus. Therefore, the rejection is maintained.

Previous rejection of Claims 24, 26-29, 32 and 35-37 under 35 U.S.C. 112, first paragraph is maintained, because the specification, while being enabling for a method of treatment of human malignancies comprising administering a pegylated form of the human arginase I of SEQ ID NO: 9, does not reasonably provide enablement for a method of treatment of any malignancies, comprising administering any modified human arginase I or any composition comprising any chemically modified human arginase I or any composition comprising any unknown compound that would reduce physiological arginine to levels less than 10uM for 3 days. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. This rejection has been discussed at length in the previous office action. It is maintained for the reasons of record and discussed below.

Applicants argue that the instant specification is sufficient to permit those skilled in the art to make and use the invention, wherein said invention is an isolated and purified recombinant human arginase I of at least 336 I.U./mg, 80-100% purity and an extended half-life of at least 3 days and further argue that according to MPEP 2164.01 (b), "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 USC 112 is satisfied" and the rejection is considered to be overcome.

Applicant's arguments have been fully considered but are not persuasive to overcome the scope of enablement rejection. The Examiner acknowledges MPEP 2164.01 (b), however, there is no reasonable correlation between what is disclosed in the specification and entire scope of the claims for enabling the full scope of the claimed invention. Claims are so broad as to encompass

a method of treatment of any malignancies using any human arginase modified by any chemical modification or any composition comprising any compound that would reduce physiological arginine to less than 10 uM for 3 days. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of chemical modifications of any human arginase encompassing amidation, acylation, glycosylation, SH group modification by N-ethylmaleimide (NEM), methylation or pegylation broadly encompassed by the claims as well as any unknown compound which is required (claims 28-29) in a composition for reducing physiological arginine to less than 10 uM. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only one human arginase and modification for pegylation of said arginase by treating with polyethylene glycol.

The specification does not support the broad scope of the claims which encompass a method of treatment of any malignancies using any modified human arginase I by any chemical modification because the specification does **not** establish: (A) regions of the protein structure which may be modified without affecting arginase activity; (B) the general tolerance of arginase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any arginase amino acid residues with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

The specification does not also support the broad scope of the claims which encompass a method of treatment of any malignancies using any composition comprising any unknown compound to reduce physiological arginine level because the specification does **not** establish: (A) what the compounds are; or (B) the structural features of said unknown compounds that

correlate with the required activity (i.e., reduction of physiological arginine levels less than 10 uM for 3 days.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including a method of treatment of any malignancies using any compound that reduces physiological arginine to less than 10 uM for 3 days. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of any modified arginase I and an unknown compound for reducing physiological arginine level having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). Therefore, the rejection is maintained.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Previous rejection of Claims 28, 29 and 37 under 35 U.S.C. 102(e) as being anticipated by Tepic et al. (WO/2003/063780, publication 7/8/2003, claim priority of provisional application 60/350,971 filed on 1/25/2002, see IDS) is maintained.

Applicants argue that independent Claim 24 has been amended to recite an "isolated and purified recombinant human arginase I, wherein said arginase comprising chemical modification resulting in a specific activity of at least 336 I.U./mg, a purity of 80-100% and an extended half-life for at least 3 days". Applicant submits that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference" and further argue that Tepic et al. discloses no chemically modified, isolated and highly purified recombinant human arginase I with specific activity of at least 336 I.U/mg and half-life for at least 3 days.

Applicant's arguments have been fully considered but are not persuasive because claim 28 is not dependent on claim 24 and the limitations that are present in claim 24 are not present in claim 28. Therefore, previous rejection of claims 28, 29 and 37 is maintained as there is no amendment (or substantial amendment) in said claims.

As discussed previously, Tepic et al. teach a therapeutic composition and a method for the treatment of cancer by depletion of arginine without systemic complications with said composition wherein the composition comprises an arginine decomposing enzyme i.e. type I liver human arginase, wherein the enzyme is partially purified and recombinant (abstract and p7, paragraph 1 and 2). Tepic et al. also teach that the enzyme is modified by pegylation to increase circulation half-life. Tepic et al. also teach that said composition may be administered as a drug for treating cancer including liver cancer, to reduce arginine level below 10 uM for at least 72 hr (3 days).

Withdrawn-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the

basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Previous rejection of claims 24, 26-27, 32 and 35-36 under 35 U.S.C. 102(e) as being anticipated by Tepic et al. (WO/2003/063780, publication 7/8/2003, claim priority of provisional application 60/350,971 filed on 1/25/2002, see IDS) is withdrawn in view of applicant's amendment of claim 24 by adding limitation of 80-100% purity, which is not explicitly taught by Tepic et al.

New-Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24, 26-27, 32 and 35-36 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tepic et al. (WO/2003/063780, publication 7/8/2003, claim priority of provisional application 60/350,971 filed on 1/25/2002, see IDS) in view of Ikemoto et al. (Expression of human liver arginase in Escherichia coli. Purification and properties of the product, Biochem J. 1990 Sep 15; 270(3): 697-703, see IDS). The instant claims are drawn to a method of treatment of human malignancies, comprising administering an isolated and purified recombinant human arginase I to a patient, wherein said arginase comprises any chemical modification resulting in a specific activity of at least 336 I.U./mg, a purity of 80-100%, and an extended half life, or any composition comprising an unknown compound that reduces the physiological arginine levels to 10 uM for 3 days, wherein said human malignancies are selected from the group consisting of: liver tumor, breast cancer, and rectal cancer and the human arginase I is modified by pegylation i.e. treating with polyethylene glycol.

Tepic et al. teach a therapeutic composition and a method for the treatment of cancer by depletion of arginine without systemic complications comprising the administration of an arginine decomposing enzyme i.e. type I liver human arginase, wherein the enzyme is isolated, recombinantly produced and partially purified to have a specific activity of 389 I.U./mg of protein (see p25, Example 10 of specification of the instant application). The enzyme of Tepic et al. is 77% pure as calculated by the instant application (see remark section of documents submitted on 7/6/2007). Tepic et al. also teach that the enzyme is modified by pegylation to increase circulation half-life. Tepic et al. also teach that said composition may be administered as a drug for treating cancer including liver cancer. Tepic et al. do not teach that said human arginase is 80-100% pure.

Ikemoto et al. teach a human arginase I, cloning, expression and a method of producing the recombinant arginase in E. coli and purification by ion exchange DEAE-cellulose column chromatography followed by Sephadex column chromatography and finally with agar-gel electrophoresis resulting in 10 mg arginase per 1 gm of E. coli cells, which according to applicant is 77% pure (see remark section of documents submitted on 7/6/2007), since Tepic et al. used the arginase of Ikemoto et al.

By combining the teachings of Tepic et al. and Ikemoto et al., it would have been obvious to one to ordinary skill in the art at the time of the invention was made to purify the arginase of Ikemoto et al. in a more pure form, i.e. more than 80% pure by using affinity chromatography, to make a highly pure arginase protein to be used in the method of treating cancer taught by Tepic et al.

One of ordinary skill in the art would have been motivated to purify the human arginase in a highly pure form by using affinity chromatography to use in industrial and medical applications.

One of ordinary skill in the art would have a reasonable expectation of success in further purifying the human arginase I by making a fusion protein with a His tag and using commercial affinity chromatography kits for purifying a His tagged fusion protein comprising the human arginase to achieve a highly pure human arginase for using in a composition for treating cancer.

Therefore, the invention of claims 24, 26-27, 32 and 35-36 would have been prima *facie* obvious to one of ordinary skill in the art.

Conclusion

Status of the claims:

Claims 24, 26-29, 32, and 35-37 are pending.

Claims 24, 26-29, 32, and 35-37 are rejected.

No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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